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PATENT SPECIFICATION (11) 1 582 853

1 582 853

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(72) Inventors JEAN BOWLER

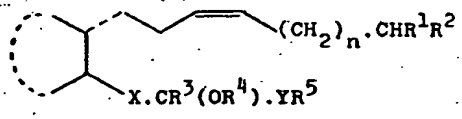
(19)

(54) PROSTANE DERIVATIVES

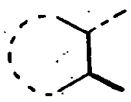
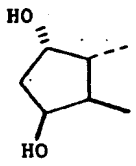
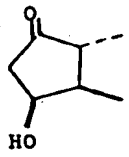
(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel prostane derivatives, and in particular it relates to novel 4-prostene derivatives possessing high luteolytic activity. The new compounds are therefore useful as contraceptives of for control of the oestrous cycle in animals. The compounds may also be useful for the induction of labour or the early termination of pregnancy, or as hypotensives, for the relief of bronchospasm or the inhibition of gastric acid production.

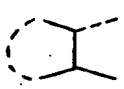
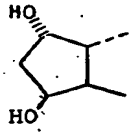
According to the invention there is provided a prostane derivative of the formula:—



I

wherein either  represents  or 

and R^1 is a carboxy radical, or a C_{2-12} alkoxycarbonyl radical, or

 represents 

and R^1 is a hydroxymethyl or C_{2-12} alkoxymethyl radical, R^2, R^3 and R^4, which may be the same or different, are each a hydrogen atom or a C_{1-5}alkyl radical, X is an ethylene or *trans*-vinylene radical, Y is a C_{1-6}alkyleneoxy radical, wherein the oxygen atom is bonded to R^5, R^5 is a phenyl or naphthyl radical which is unsubstituted or is substituted by one or more substituents selected from halogen atoms, nitro radicals and C_{1-5}alkyl, alkoxy and halogenoalkyl radicals, and n is 1 to 4, and for those compounds wherein R^1 is a carboxy radical, the pharmaceutically or veterinarily acceptable salts thereof.

A suitable value for R^1 when it is a C_{2-12}alkoxycarbonyl radical is, for example, a methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl or decyloxycarbonyl radical, especially such a radical of 2 to 5 carbon atoms, and particularly a methoxycarbonyl radical; and a suitable value for R^1 when it is a C_{2-12}alkoxymethyl radical is, for example, a methoxymethyl, ethoxymethyl, butoxymethyl or decycloxymethyl radical, especially such a radical of 2 to 5 carbon atoms.

A suitable value for any of R^2, R^3 and R^4 when it is a C_{1-5}alkyl radical is, for example, a methyl, ethyl, propyl, butyl or pentyl radical, especially a methyl or ethyl radical and particularly a methyl radical.

n is preferably 1 or 2.

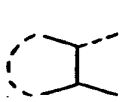
A suitable value for Y is, for example, a methylenoxy, ethylenoxy, trimethyleneoxy, ethylideneoxy, isopropylideneoxy [—$C(CH_3)_2O$—], propylideneoxy, 1-methylpropylideneoxy [—$C(CH_3)(C_2H_5).O$—] or 1-ethylpropylideneoxy [—$C(C_2H_5)_2.O$—] radical, particularly a methyleneoxy or isopropylideneoxy radical.

A suitable halogen substituent in R^5, is, for example, a chlorine, fluorine, bromine or iodine atom, especially a chlorine atom; a suitable C_{1-5}-alkyl or alkoxy substituent in R^5 is, for example, a methyl, ethyl, methoxy or ethoxy radical; and a suitable C_{1-5} halogenoalkyl substituent is, for example, a chloroalkyl or fluoroalkyl radical, such as a trifluoromethyl radical. Preferred values for R^5 contain not more than two substituents, and particular values are pehnyl, chlorophenyl, especially 3-chlorophenyl, and trifluoromethylphenyl, especially 4-trifluoromethylphenyl, radicals.

A suitable pharmaceutically or veterinarily acceptable salt is, for example, an ammonium, alkylammonium containing 1 to 4 C_{1-5}alkyl radicals, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, or alkali metal salt, for example an ammonium, triethylammonium, ethanolammonium, diethanolammonium, sodium or potassium salt.

It will be observed that the novel prostane derivatives of the formula I contain at least three asymmetrically substituted carbon atoms, namely the two carbon atoms at which the side-chain are attached to the ring (the relative stereochemistry at these two positions is fixed in formula I) and the carbon atom of the group —$CR^5(OR^6)$— in the lower side-chain. In addition, carbon atoms 2, 9 and 11 may also be asymmetrically substituted, so that it is clear that the compounds of the invention may exist in racemic or in optically active form. It is to be understood that the useful bioligical properties of a racemic compound, comprised of I and its mirror image, may be present to differing extents in the optical isomers, and that this invention relates to racemates and to any optically active form which shows the same useful properties, it being a matter of common general knowledge how the optically active forms may be obtained, and their bioligical properties determined. It is also to be understood that this invention relates to both C—15 epimers, that is, epimers at the —$CR^3(OR^4)$— carbon atom in the lower side chain.

A preferred group of prostane derivatives of the invention having high luteolutic activity comprises compounds of the formula I wherein R^1 is a carboxy, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl or methoxymethyl radical, R^2, R^3 and R^4, which may be the same or different, are each a hydrogen atom or a methyl radical,



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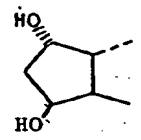
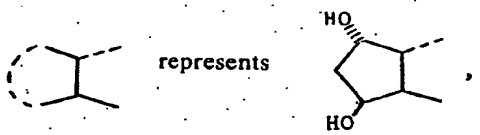


X is a *trans*-vinylene radical, Y is a methyleneoxy or idopropylideneoxy radical, n is 1, and R^5 has the meaning stated above, particularly a phenyl radical, a halogenophenyl radical, for example a chlorophenyl radical, or a halogenoalkylphenyl radical, for example a trifluoromethylphenyl radical, and especially a phenyl, 3-chlorophenyl or 4-trifluoromethylphenyl radical. Preferred compounds in this group are methyl 16 - (4 - chlorophenoxy) - 19α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* -

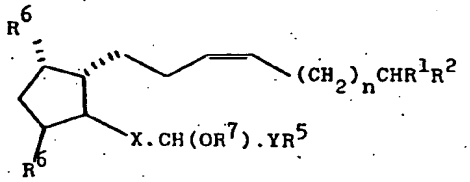
prostadienoic acid, and 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 4 - *cis*,13-*trans* - prostadien - 1,9α,11β,15α - tetraol.

The novel prostane derivatives of the invention may be manufactured by methods known in themselves for the manufacture of chemically analogous compounds. Thus, the following processes are provided as a further feature of the invention, wherein R^1, R^2, R^3, R^4, R^5, n, X and Y have the meanings stated above, unless defined otherwise:—

(a) for those compounds wherein



and R^3 is a hydrogen atom, the hydrolysis, for example with an acid, such as acetic acid, of a compound of the formula:—

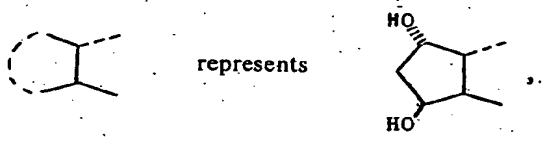


II

wherein R^6 is a tetrahydropyran - 2 - yloxy radical and R^7 is a tetrahydropyran - 2 - yl radical or a C_{1-5}alkyl radical;

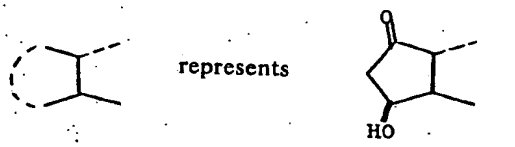
(b) for those compounds wherein R^1 is an alkoxycarbonyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^1 is a carboxy radical with a C_{1-11} diazoalkane, or of a salt thereof with a C_{1-11} alkyl halide, for example an alkyl iodide or alkyl bromide;

(c) for those compounds wherein R^1 is a hydroxymethyl radical and

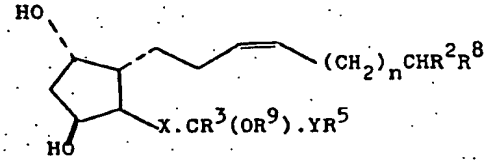


the reduction, for example with a complex metal hydride such as lithium aluminium hydride, of the corresponding prostane derivative of the formula I wherein R^1 is an alkoxycarbonyl radical;

(d) for those compounds wherein



and R^3 is an alkyl radical, the oxidation, for example with chromium trioxide/pyridine complex, or Jones's reagent (chromic acid in acetone), of a compound of the formula:—



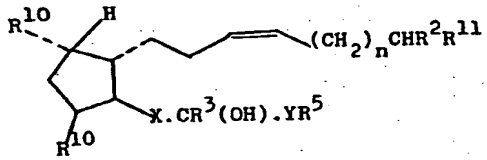
III

wherein R^3 is a C_{1-5}alkyl radical, R^8 is a C_{2-12}alkoxycarbonyl radical or a tri(C_{1-5}-alkyl)silyloxycarbonyl radical, and R^9 is a C_{1-5}alkyl or tri(C_{1-5}-alkyl)silyl radical, or a tetrahydropyran - 2 - yl radical, whereafter if necessary the protecting silyl or tetrahydropyran - 2 - yl groups are hydrolysed by treating the product so obtained with an acid;

(e) for those compounds wherein R^4 is an alkyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^4 is a hydrogen atom with an alkyl halide, for example an alkyl iodide, in the presence of one molecular proportion of a strong base, for example sodium hydride;

(f) for those compounds wherein

and R^3 is a C_{1-5}alkyl radical, the hydrolysis, with an acid, of a silyl derivative of the formula:—

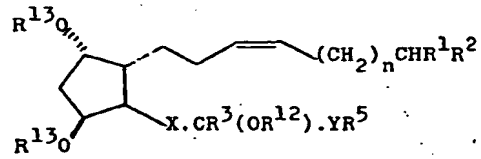


IV

wherein R^{10} is a tri(C_{1-5}alkyl)silyloxy radical, R^3 is a C_{1-5}alkyl radical and R^{11} is a tri(C_{1-5}alkyl)silyloxycarbonyl, tri(C_{1-5}alkyl)silyloxymethyl, C_{2-12}alkoxycarbonyl or C_{2-12}-alkoxymethyl radical;

(g) for those compounds wherein

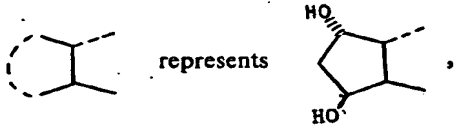
R^1 is a carboxy or alkoxycarbonyl radical, and R^4 is a hydrogen atom, the hydrolysis with alkali of a compound of the formual:—



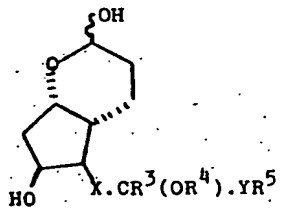
V

wherein R^2, R^3, R^5, X and Y have the meanings given above, R^1 is a carboxy or a C_{2-12}alkoxycarbonyl radical, R^{12} is a hydrogen atom, when R^3 is an alkyl radical, or a carboxylic acyl radical such as a acetyl, benzoyl or *p*-phenylbenzoyl radical, when R^3 is a hydrogen atom, and R^{13} is a carboxylic acyl radical such as an acetyl, benzoyl or *p*-phenylbenzoyl radical;

(h) for those compounds wherein R^1 is a carboxy radical, and



the reaction of a lactol of the formula:—



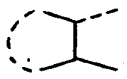
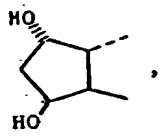
VI

with a triphenylphosphonium salt of the formula $Ph_3\overset{+}{P}.(CH_2)_{n+1}CHR^2.COOH.Z^-$ wherein Z^- is an anion, for example bromide, in the presence of a strong base. (i) for those compounds wherein R^1 is a carboxy radical, the hydrolysis of a corresponding compound of the formula I wherein R^1 is an alkoxycarbonyl radical.

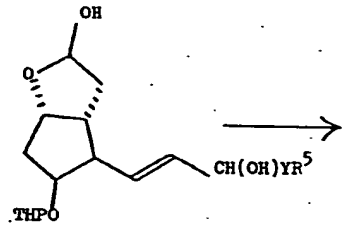
A starting material of the formula II may be obtained by reacting the known lactol VII with methyltriphenylphosphonium bromide in the presence of a strong base to give the allyl derivative VIII, which is treated with 2,3 - dihydropyran to give the tris(tetrahydropyran - 2 - yl) derivative IX. IX is reacted with borane in the presence of alkaline hydrogen peroxide to give the primary alcohol X, the primary alcohol X is oxidesed with Collins' reagent to the aldehyde XI is subjected to a Wittig reaction with a triphenylphosphonium bromide derivative, $PH_3P^+.(CH_2)_{n+1}CHR^2COOH.Br^-$, in the presence of a strong base to give the required starting material of the formula II, wherein X is a *trans*-vinylene radical and R^7 is a tetrahydropyran - 2 - yl radical.

Starting materials of the formula II wherein X is an ethylene radical may be prepared by a sequence of reactions similar to that described above, but starting from the corresponding known saturated lactol in place of the unsaturated lactol VII.

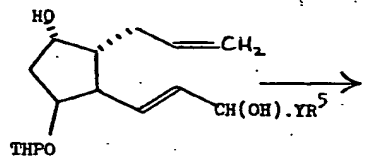
The starting material of the formula III may be obtained by selective silylation of the corresponding prostane derivative of the invention wherein

 represents  ,

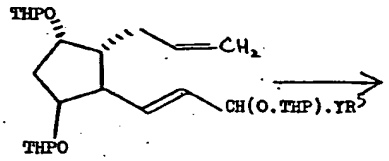
with, for example, tri(C_{1-6}alkyl)silyl



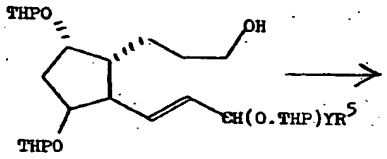
VII



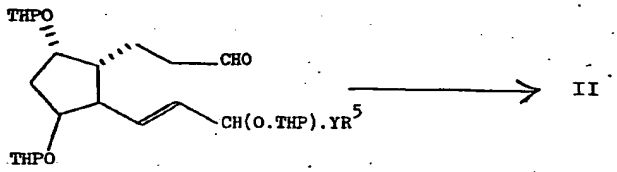
VIII



IX



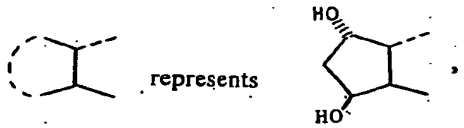
X



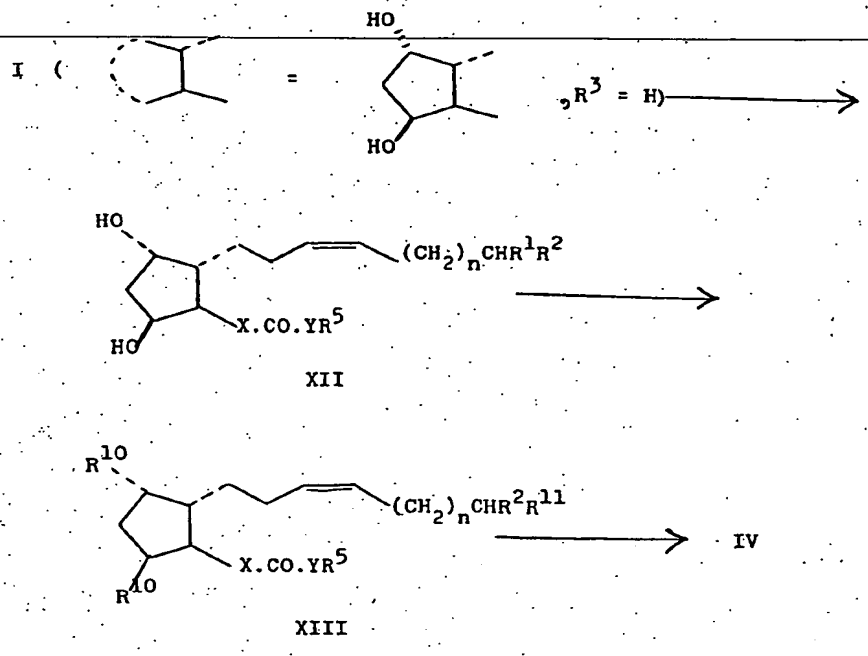
XI

amide, such as diethylamino-dimethyl-t-butylsilane.

The starting material of the formula IV may be obtained from the corresponding compound of the formula I wherein

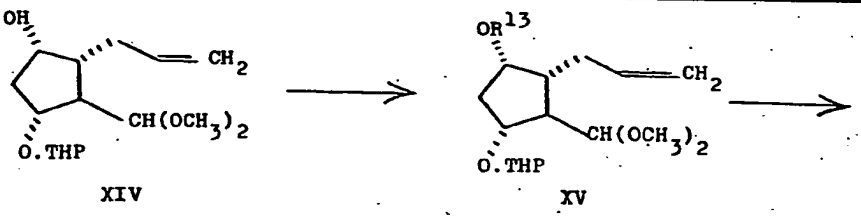


and R^3 is a hydrogen atom, by selective oxidation with one equivalent of Jones' reagent to give a ketone XII, which is treated with an excess of a silylating agent, for example a tri(C_{1-6}alkyl)silylamide, to protect the C—9 and C—11 hydroxy radicals, and the carboxy radical if present, giving the silyl derivative XIII. The silyl derivative XIII is then treated with a C_{1-6} alkylmagnesium halide to give the required starting material IV.

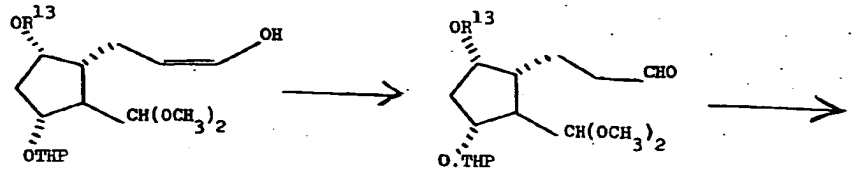


The starting material of the formula V may be obtained by treating the known acetal XIV with an acid chloride, $R^{13}Cl$, in pyridine to give the protected acetal XV, which is reacted with borane and alkaline hydrogen peroxide to give the alcohol XVI. The alcohol XVI is oxidised to the aldehyde XVII with Collin's reagent, and the aldehyde XVII is reacted with a phosphonium salt, $Ph_3P(CH_2)_2CHR^1R^2$, in the presence of a base to give the olefin XVIII, which is hydrolysed selectively, for example with concentrated hydrochloric acid and 2% v/v of isopropanol in chloroform, to the hydroxy-aldehyde XIX. The hydroxy-aldehyde XIX is treated with a phosphonate reagent, $(CH_3O)_2PO.CH_2CO.YR^5$, to give an enone XX, and the enone XX is reduced with a Meerwein-Ponndorf reagent to the diol XXI, which is epimerized by reaction with diethyl azodicarboxylate, triphenylphosphine and a carboxylic acid, $R^{13}OH$, to a starting material V, (R^{12} = R^{13} = carboxylic acyl, X = *trans*-vinylene).

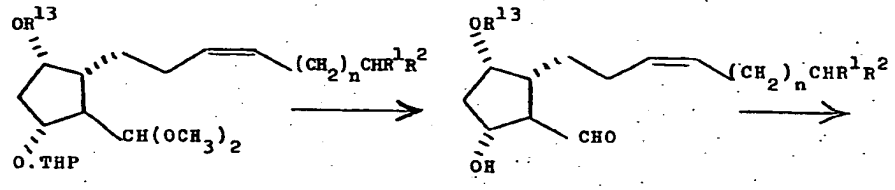
Starting materials of the formula V wherein R^3 is an alkyl radical may be obtained by reacting the enone XX with dihydropyran to give a tetrahydropyranyl ether or with a silylating agent to give a silyl ether XXII, which is treated with a Grignard reagent R^3MgBr to give an enol XXIII, the protecting tetrahydropyranyl or trialkylsilyl group is hydrolysed, and the diol XXIV is epimerized in the reaction described above to give a starting material V (R^{12} = hydrogen, R^{13} = carboxylic acyl, X = *trans*-vinylene).



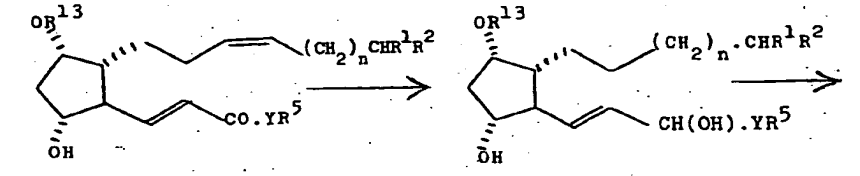
XIV XV



XVI XVII



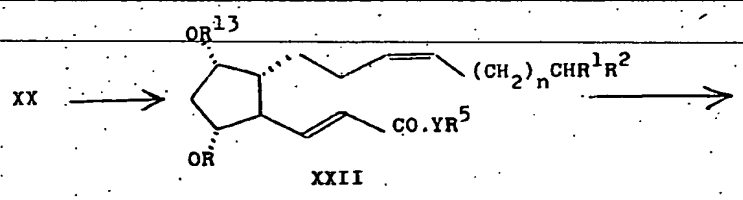
XVIII XIX



XX XXI

→ V ($R^{12} = R^{13}$ = carboxylic acyl, X = *trans*-vinylene) THP = tetrahydropyran - 2 - yl

Corresponding starting materials V wherein X is an ethylene radical may be obtained in a completely analogous manner, but carrying out the reduction of the enone XX with sodium borohydride instead of with a Meerwein-Ponndorf reducing agent.



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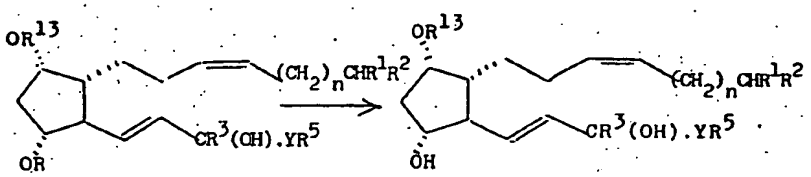
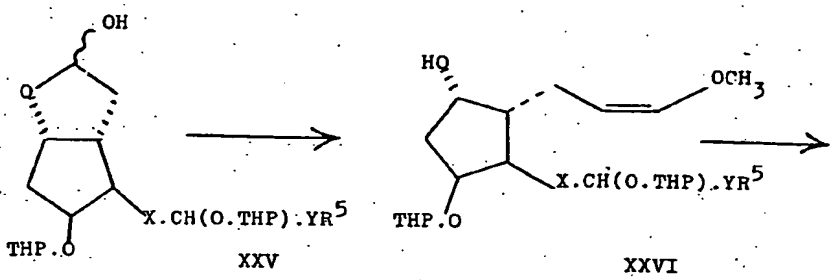


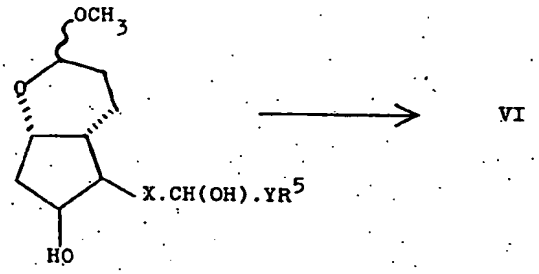
XXIII XXIV

→ V (R^{12} = H, R^{13} = carboxylic acyl, X = *trans*-vinylene) R = tetrahydropyran - 2 - yl or trialkylsilyl.

The starting material of the formula VI may be obtained from known bis(tetrahydropyranyl) derivatives XXV, by reaction thereof with a (methoxymethyl)triphenylphosphonium salt in the presence of a strong base to give an olefin XXVI, which on treatment at pH 2 with hydrochloric acid/potassium chloride buffer in methanol gives a compound XXVII. Further treatment of the compound XXVII at pH 1 with hydrochloric acid/potassium chloride buffer in tetrahydrofuran removes the protecting methyl group to give the required lactol starting material VI.



XXV XXVI



XXVII VI

It is to be understood, of course, that an optically active prostane derivative of the invention may be obtained either by resolving the corresponding racemate, or by resolving a suitable starting material or other intermediate in the preparative reaction sequence.

As stated above, the prostane derivatives of the invention possess luteolytic properties, and in particular they are more active as luteolytic agents and less active as smooth muscle stimulants than the naturally occurring prostaglandins. Thus, for example, methyl 16 - (4 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate is approximately 100 times as active as natural prostaglandin $F_2\alpha$ as a luteolytic agent in hamsters (subcutaneous dosing) but possesses only approximately one twentieth of the smooth muscle stimulant activity.

When a prostane derivative of the invention is to be used for the induction of labour, it is used in the same way as it is known to use the naturally occurring prostaglandin E_2, that is by administering a sterile substantially aqueous solution containing from 0.01 to 10μg./ml., preferably 0.01 to 1 μg./ml. of the compound, by intravenous infusion, or by transcervical extra-amniotic or intra-amniotic infusion until labour commences. Also, for this purpose, the prostane derivatives of the invention may be used in combination or concurrently, with a uterine stimulant, for example oxytocin, in the same way as it is known to use the natural prostaglandin in combination, or concurrently, with oxytoxin for the induction of labour.

Certain of the compounds, including those wherein R^1 is a phydroxymethyl radical, are particularly effective when dosed orally. When a prostane derivative of the invention is to be used for control of the oestrus cycle in animals, for example cattle or horses, it is used in the same way as it is known to use the prostaglandin derivatives known as cloprostenol and fluprostenol for this purpose. The compounds may be used for this purpose in combination, or concurrently, with a gonadotrophin, for example pregnant mare serum gonadotrophin (PMSG) or human chorionic gonadotrophin (HCG) to hasten the onset of the next cycle.

Thus, according to a further feature of the invention there is provided a pharmaceutical or veterinary composition comprising a prostane derivative of the formula I together with a pharmaceutically or veterinarily acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example tablets or capsules, in a form suitable for inhalation, for example an aerosol or a solution suitable for spraying, in a form suitable for infusion, for example sterile, substantially aqueous, or oily, solutions or suspensions, or in the form of a suppository or pessary, suitable for anal or vaginal use.

The compositions of the invention may be prepared by conventional means, and may contain conventional excipients.

The composition is preferably in the form of a tablet, capsule or a substantially aqueous, sterile solution, and a particular preferred composition is a substantially aqueous, sterile solution containing from 25 to 150 μg./ml., preferably from 25 to 75 μg./ml.

The invention is illustrated, but not limited by the following Examples. Throughout the Examples, R_f values refer to silica gel plates supplied commercially by Merck (trademark) of Darmstadt, and the spots were visualised either by fluorescence under ultravoilet radiation, by exposure to iodine vapour, or by spraying the plates with a solution of ceric ammonium nitrate in sulphuric acid and heating. Organic solutions were dried with anhydrous magnesium sulphate.

Example 1.

To a solution of 16 - (3 - chlorophenoxy) - 9α,11β,15α - tris(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid (78 mg.) on dry methanol (1.2 ml.) was added toluene-*p*-sulphonic acid (116 μl. of a 1% w/v solution in tetrahydrofuran) and the mixture was stirred at room temperature for 16 hours. Pyridine (3 drops) was added and the solvents were evaporated. The residue was extracted with diethyl ether (40 ml.) and washed successively with saturated sodium bicarbonate solution and brine. Evaporation of the solvent gave methyl 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate. Purification by thin layer chromatography on silica gel plates using 3% v/v acetic acid in ethyl acetate as the developing solvent gave the pure compound, R_f=0.2. The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):—

6.85—7.3, multiplet, 4 aromatic protons

5.1—6.05, multiplet, 4 aromatic protons

3.9—4.5, multiplet, 5H, —CH—O—

3.62, singlet, 3H, methyl ester.

The mass spectrum of the tris(timethylsilyl) derivative showed $(M—CH_3)^+ = 639.2761$ (calculated for $C_{33}H_{52}ClO_6Si_3 = 639.2756$).

The tris(tetrahydropyranyl ether) used as starting material may be obtained as follows:—

Finely powdered methyluriphenylphosphonium bromide (536 mg.) was dried under vacuum for 1 hour and then dissolved in dimethyl sulphoxide (1.5 ml.), and the solution was cooled to room temperature. To this solution was added 0.625 ml. of a 2M solution of methanesulphinylmethyl sodium in dimethyl sulphoxide, followed by a solution of 4β - [4 - (3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 2,3,3aβ, 6aβ - tetrahydro - 2 - hydroxy - 5β - (tetrahydropyran - 2 - yloxy)cyclopenteno[b] - furan (254 mg.) in a mixture of dimethyl sulphoxide (2.5 ml.) and toluene (1 ml.). The solution was stirred for 2 hours, and the solvent was evaporated under reduced pressure. The residue was shaken with water (1 ml.) and diethyl ether (5 ml.), and the aqueous phase was separated and re-extracted with diethyl ether (6 x 2 ml.). The combined ether extracts were washed with saturated brine and dried, and the solvent was evaporated. The residue was chromatographed on silica gel (80 g.), and elution with 50% v/v ethyl acetate in toluene gave the allyl derivative, 2α - allyl - 3β - [4 - (3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 4β - (tetrahydropyran - 2 - yloxy)cyclopentan - 1α - ol, $R_F = 0.5$ (50% v/v ethyl acetate in toluene).

To a solution of the allyl derivative (212 mg.) in methylene chloride (4.2 ml.) under an atmosphere of nitrogen was added successively redistilled 2,3-dihydropyran (192 μl.) and a solution of anhydrous toluene - *p* - sulphonic acid in tetrahydrofuran (84 μl. of a 1% w/v solution). After 10 minutes, pyridine (1 drop) was added, followed by ethyl acetate (20 ml.). The solution was washed successively with saturated sodium bicarbonate solution and brine, and was dried, and evaporation of the solvents gave the tris(tetrahydropyranyl ether). 2α - allyl - 3β - [4 - (3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 1α,5β - bis(tetrahydropyran - 2 - yloxy) - cyclopentane, $R_F = 0.6$ (25% v/v ethyl acetate in toluene).

To a solution of the tris(tetrahydropyranyl ether), (59 mg.), in dry tetrahydrofuran (2 ml.) under an atmosphere of argon at 0°C. was added 80 μl. of a 1M solution of borane in tetrahydrofuran. After 3 hours, water (0.16 ml.), 1N sodium hydroxide (0.16 ml.) and 30% w/v hydrogen peroxide (0.4 ml.) were added successively, and the mixture was stirred at 0°C. for 30 minutes. The reaction mixture was diluted with water (10 ml.) and extracted with methylene chloride (4 x 25 ml.). The organic extracts were washed successively with dilute sodium sulphite solution, sodium bicarbonate solution and brine, and were then dried, and the solvents were evaporated to give the primary alcohol, 3 - [2β - [4 - (3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 3β,5α - bis-(tetrahydropyran - 2 - yloxy)cyclopent - 1α - yl]propanol, $R_F = 0.3$ (50% v/v ethyl acetate in toluene).

A solution of the primary alcohol (119 mg.) in methylene dichloride (2 ml.) was added to a stirred 0.5M solution of Collins' reagent (3.1 ml.). After 15 minutes at room temperature, the mixture was poured onto a column of "Florisil" (trade mark) magnesium silicate (14 g.), and eluted with 20% v/v ethyl acetate in methylene dichloride to give the aldehyde, 3 - [2β - [4 - (3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 3β,5α - bis(tetrahydropyran - 2 - yloxy)cyclopent - 1α - yl]propionaldehyde, $R_F = 0.6$ (50% v/v ethyl acetate in toluene).

Finely powdered (3 - carboxypropyl)triphenylphosphonium bromide (320 mg.) was heated to 100°C. under vacuum for 1 hour. The evacuated vessel was filled with an atmosphere of dry nitrogen, the solid was dissolved in dimethyl sulphoxide (3 ml.) and the solution was cooled to room temperature. To this solution was added 0.75 ml. of a 2M solution of methanesulphinylmethyl sodium in dimethyl sulphoxide, followed by a solution of the aldehyde described above (112 mg.) in a mixture of dimethyl sulphoxide (5 ml.) and toluene (2 ml.) The solution was stirred for 3 hours, and the solvent was evaporated under reduced pressure at a temperature below 40°C. The residue was shaken with water (2 ml.) and extracted with water (5 x 10 ml.) and the extracts were discarded. The aqueous

solution was acidified to pH 3—4 with 2N aqueous oxalic acid, and extracted with a mixture of equal parts of ether and petroleum ether (b.p. 40—60°C., 5 x 6 ml.). The extracts were combined, washed with saturated brine and dried, and evaporation of the solvents gave the acid, 16 - (3 - chlorophenoxy) - 9α,11β,15α - tris(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid, $R_f = 0.5$ (50% v/v ethyl acetate in toluene).

Example 2.

To a solution of methyl 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate (32 mg.) in diethyl ether (1 ml.) and tetrahydrofuran (1 ml.) was added lithium aluminium hydride (28 mg.). The mixture was stirred at room temperature for 10 minutes, the excess of hydride was destroyed by the addition of water (0.5 ml.), and the mixture was extracted with methylene chloride. The extracts were dried, and the solvent was evaporated to give 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadien - 1,9α,11β,15α - tetranol, $R_f = 0.3$ (5% v/v methanol in ethyl acetate).

The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):—

6.8—7.4, broad multiplet, 4H, aromatic protons

5.3—6.05, broad multiplet, 4H, olefinic protons

3.2—4.5, broad multiplet, 7H, —$\overset{\frown}{CH}$—O— + 4 exchangeable protons.

The mass spectrum of the tetra(trimethylsilyl) derivative showed $M^+ = 698.3425$ (calculated for $C_{33}H_{58}ClO_6Si_4 = 697.29991$).

Example 3.

To a solution of methyl 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate (12 mg.) on a mixture of methanol (1.37 ml.) and water (0.273) was added 0.273 ml. of a 1M solution of potassium hydroxide in methanol. The mixture was stirred at room temperature for 18 hours, acidified to pH 4.5 with aqueous oxalic acid, and diluted with ethyl acetate (40 ml.) The mixture was washed with brine, the organic phase was separated, dried, and the solvent was evaporated to give 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid, $R_f = 0.3$ (5% v/v acetic acid in ethyl acetate). The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):—

6.85—7.3, broad multiplet, 4H, aromatic protons

5.2—6.0, broad multiplet, 4H, olefinic protons

3.9—4.5, broad multiplet, 5H, —CH—O— + 4-exchangeable protons.

The mass spectrum of the tris(trimethylsilyl) derivative showed $(M—CH_3)^+ = 697.29966$ (calculated for $C_{33}H_{58}ClO_6Si_4 = 697.29991$).

Example 4.

	% w/v
16 - (3 - Chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid	0.003
Sodium phosphate B.P.	2.90
Sodium acid phosphate B.P.	0.30
Water for injection	to 100

The sodium phosphate B.P. was dissolved in about 80% of water, followed by the prostadienoic acid derivative, and when dissolved, the sodium acid phosphate

B.P. The solution was made up to volume with water for injection, and the pH was checked to be between 6.7 and 7.7 The solution was filtered to remove particulate matter, sterilised by filtration, and filled into pre-sterilised neutral glass ampoules under aseptic conditions.

The prostadienoic acid derivative may, of course, be replaced by an equivalent amount of another prostane derivative of the invention.

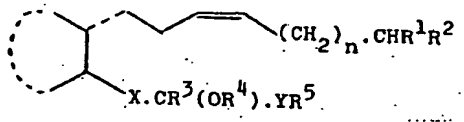
Example 5.

The process described in Example 4 was repeated, omitting the sodium phosphate B.P. and sodium acid phosphate B.P., to give ampoules containing a sterile aqueous solution of 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - pentanor - 4 - *cis*,13 - *trans* - prostadienoic acid, which are used in the manner described in Example 4.

The prostadienoic acid derivative may be replace by an equivalent amount of another prostanoic acid derivative of the invention, the give other sterile solutions.

WHAT WE CLAIM IS—:

1. A prostane derivative of the formula:—



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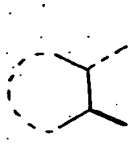
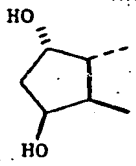
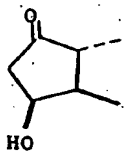
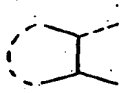
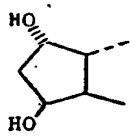
wherein either  represents  or 

and R^1 is a carboxy radical, or a C_{2-12} alkyloxycarbonyl radical, or

 represents  ,

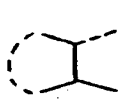
and R^1 is a hydroxymethyl or C_{2-12} alkoxymethyl radical, R^2, R^3 and R^4, which may be the same or different, are each a hydrogen atom or a C_{1-5}alkyl radical, X is an ethylene or *trans*-vinylene radical, Y is a C_{1-5}alkyleneoxy radical, wherein the oxygen atom is bonded to R^5, R^5 is a phenyl or naphthyl radical which is unsubstituted or is substituted by one or more substituents selected from halogen atoms, nitro radicals and C_{1-5}alkyl, alkoxy and halogenoalkyl radicals, and n is 1 to 4, and for those compounds wherein R^1 is a carboxy radical, the pharmaceutically or veterinarily acceptable salts thereof.

2. A prostane derivative as claimed in claim 1 wherein R^1 is a carboxy, hydroxymethyl, methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, decycloxycarbonyl, methoxymethyl, ethoxymethyl, butoxymethyl or decyloxymethyl radical, R^2, R^3 and R^4 are each a hydrogen atom or a methyl, ethyl, propyl, butyl or pentyl radical, n is 1 or 2, X has the meaning stated in claim 1, Y is a methyleneoxy, ethyleneoxy, trimethyleneoxy, ethylideneoxy, isopropylideneoxy, propylideneoxy, 1-methylpropylideneoxy or 1-ethylpropylideneoxy radical, and R^5 is a phenyl or naphthyl radical which is unsubstituted or is substituted by one or more substituents selected from chlorine, bromine, iodine and fluorine atoms, a methyl, ethyl, methoxy, ethoxy, chloroalkyl and fluoroalkyl radicals, and for those compounds wherein R^1 is a carboxy radical, the ammonium, alkylammonium containing 1 to 4 C_{1-5}alkyl radicals, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals and alkali metal salts thereof.

3. A prostane derivative as claimed in claim 1 or 2 wherein R^1 is a carboxy, hydroxymethyl or methoxycarbonyl radical, R^2, R^3 and R^4 are each a hydrogen atom or a methyl radical, X has the meaning stated in claim 1, n is 1 or 2, Y is a methyleneoxy or isopropylideneoxy radical, and R^5 is a phenyl or a chlorophenyl or trifluoromethylphenyl radical containing not more than two substituents.

4. A prostane derivative as claimed in claim 3 wherein R^5 is a 3-chlorophenyl or 4-trifluoromethylphenyl radical.

5. A prostane derivative as claimed in claim 1 wherein R^1 is a carboxy, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl or methoxymethyl radical, R^2, R^3 and R^4, which may be the same or different, are each a hydrogen atom or a methyl radical,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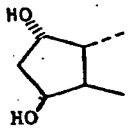

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X is a *trans*-vinylene radical, Y is a methyleneoxy or idopropylideneoxy radical, n is 1, and R^5 is a phenyl, 3-chlorophenyl or 4-trifluoromethylphenyl radical.

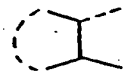
6. A prostane derivative as claimed in claim 1 which is methyl 16 - (4 - chlorophenyoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid, or 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 *trans* - prostadien - 1,9α,11β,15α - tetraol.

7. A prostane derivative as claimed in any one of claims 1 to 6 which is in racemic form.

8. A prostane derivative as claimed in any one of claims 1 to 6 which is in an optically active and luteolytically effective form.

9. A process for the manufacture of a prostane derivative as claimed in claim 1 which comprises:—

(a) for those compounds wherein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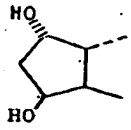

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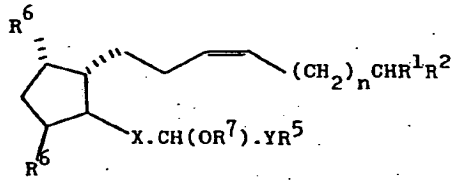
and R^3 is a hydrogen atom, the hydrolysis of a compound of the formula:—

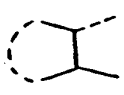


II

wherein R^6 is a tetrahydropyran - 2 - yloxy radical and R^7 is a tetrahydropyran - 2 - yl radical or a C_{1-5}alkyl radical;

(b) for those compounds wherein R^1 is an alkoxycarbonyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^1 is a carboxy radical with a C_{1-11} diazoalkane, or of a salt thereof with a C_{1-11} alkyl halide;

(c) for those compounds wherein R^1 is a hydroxymethyl radical and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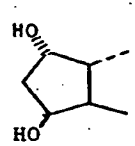

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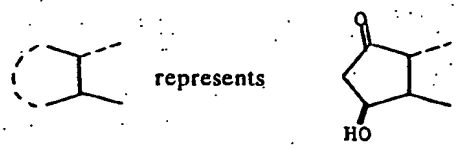
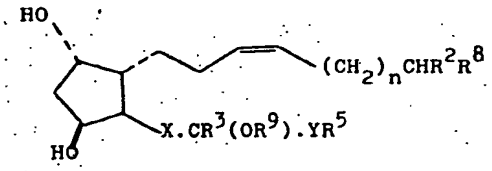
the reduction of the corresponding prostane derivative of the formula I wherein R^1 is an alkoxycarbonyl radical;
(d) for those compounds wherein

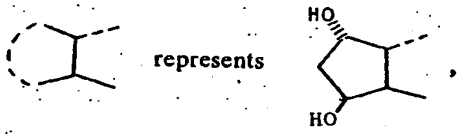


and R^3 is an alkyl radical, the oxidation of a compound of the formula:—

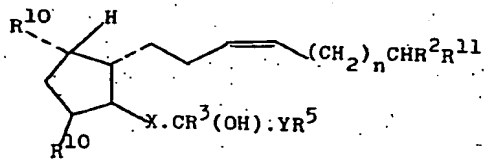


III

wherein R^3 is a C_{1-5}alkyl radical, R^8 is a C_{2-11}alkoxycarbonyl radical or a tri(C_{1-5}-alkyl)silyloxycarbonyl radical, and R^9 is a C_{1-5}alkyl or tri(C_{1-5}-alkyl)silyl radical, or a tetrahydropyran - 2 - yl radical, whereafter if necessary the protecting silyl or tetrahydropyran - 2 - yl groups are hydrolysed by treating the product so obtained with an acid;
(e) for those compounds wherein R^4 is an alkyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^4 is a hydrogen atom with an alkyl halide in the presence of one molecular proportion of a strong base;
(f) for those compounds wherein

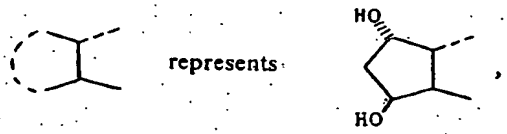


and R^3 is a C_{1-5}alkyl radical, the hydrolysis, with an acid, of a silyl derivative of the formula:—

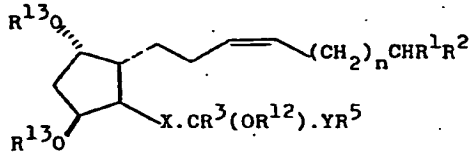


IV

wherein R^{10} is a tri(C_{1-5}-alkyl)silyloxy radical, R^3 is a C_{1-5}alkyl radical and R^{11} is a tri(C_{1-5}alkyl)silyloxycarbonyl, tri(C_{1-5}alkyl)silyloxymethyl, C_{2-12}alkoxycarbonyl or C_{2-12}alkoxymethyl radical;
(g) for those compounds wherein



R^1 is a carboxy or alkoxycarbonyl radical, and R^4 is a hydrogen atom, the hydrolysis with alkali of a compound of the formula:—

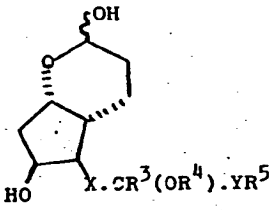


V

wherein R^1 is a carboxy or a C_{2-12}alkoxycarbonyl radical, R^{12} is a hydrogen atom, when R^3 is an alkyl radical, or a carboxylic acyl radical when R^3 is a hydrogen atom, and R^{13} is a carboxylic acyl radical;

(h) for those compounds wherein R^1 is a carboxy radical, and

the reaction of a lactol of the formula:—



VI

with a triphenylphosphonium salt of the formula $Ph_3\overset{+}{P}.(CH_2)_{n+1}CHR^2.COOH.Z^-$, wherein Z^- is an anion in the presence of a strong base; or (i) for those compounds wherein R^1 is a carboxy radical, the hydrolysis of a corresponding compound of the formula I wherein R^1 is an alkoxycarbonyl radical; and wherein R^1, R^2, R^3, R^4, R^5, n, X and Y, unless otherwise defined, have the meanings stated in claim 1.

10. A pharmaceutical or veterinary composition comprising a prostane derivative as claimed in claim 1 together with a pharmaceutically or veterinarily acceptable diluent or carrier.

11. A prostane derivative as claimed in claim 1 substantially as hereinbefore described in any one of Examples 1 to 3.

12. A process as claimed in claim 9 substantially as hereinbefore described in any one of Examples 1 to 3.

13. A pharmaceutical or veterinary composition as claimed in Claim 10 substantially as hereinbefore described in Example 4. or 5.

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